



Soldiers of Science: A Profile

RENDEZVOUS WITH A PIONEER: PROFESSOR KUPPAMUTHU DHARMALINGAM

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Abstract: This article enlightens the influential role of a great Indian scientist and teacher, Prof. K Dharmalingam in the field of bacteriophage genetics, microbiology, biotechnology and clinical proteomics. He is a role model to all those young investigators who are extremely impelled to try novel things in Science. His journey originating from yeast mitochondriogenesis to *Mycobacterium leprae* biomarkers shows how passionate he is to ameliorate his intellectual abilities and endeavor his ideas. Not only a great achiever, he is also a modest human being who always acknowledges his school teachers, PhD mentor as well as graduate students for his immense success in scientific career. He has tried to explore the cross talk between microorganisms, proteins and nucleic acids to understand the molecular machinery inside a cell.

Keywords: Prof K. Dharmalingam; clinical proteomics; Indian scientist; geneticist; biotechnologist

Childhood and early life

Prof. Kuppamuthu Dharmalingam was born on 3rd January in the year 1949 at a small village near Pollachi. He started his primary education at Gandhi Kala Nilayam High School situated on the main highway between Udumalpet and Yanamalai in Pollachi district. The curious and enthusiastic boy used to take the trouble of walking 5 km daily to learn and popularized himself as a 'good student' in the school. The child did not have a smooth journey in the beginning since he lost his mother at the age of three and his father did not have plenty of resources to support his higher education. However, he did not lose his passion for studies under these critical circumstances and completed his pre-university education after qualifying Secondary

School Leaving Certificate. Though he studied in a Tamil medium school he never had any difficulty in terms of understanding or writing English. In those days biology was not a well-nurtured area and high throughput facilities were not available. The motivated boy took up B.Sc in Zoology following his teacher's advice, while all his contemporary classmates were interested in earning more through lucrative career. After this, his academic career flourished as he became university topper at Thiagarajar College, Madurai in M.Sc. Zoology. He decided to carry on with his dream of learning 'something new' and hence he joined Dr. J. Jayaraman at Madurai Kamaraj University (MKU) to study yeast mitochondrial membrane biogenesis.

Life during PhD

The major turning point was the abrupt transition for a Zoologist into the field of Biochemistry. He joined as the first graduate student of Dr. Jayaraman when he was just setting up the lab and eventually did some extraordinary work with

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him in the early 1970s. They proposed that glucose might have a repressive action on mitochondriogenesis. The possible explanation that they gave was that glucose might induce phospholipases that disintegrate mitochondrial membrane (Dharmalingam and Jayaraman, 1971). They also tried to propose a model for concomitantly increasing mitochondrial population in a synchronously growing yeast cell population (Dharmalingam and Jayaraman, 1973).

KD: The geneticist

Having a doctoral training as a biochemist he went on to Boston and worked with a famous scientist Dr. Edward B. Goldberg at Tufts University School of Medicine in the field of bacteriophage genetics. After few years of struggle he showed that T4 bacteriophage genome requires certain modifications to survive inside the host cell and a phage coded protein is responsible for this (Dharmalingam and Goldberg, 1976a). They together published their discoveries reporting that certain modifications in the T4 phage DNA can affect late gene expression (Dharmalingam and Goldberg, 1979). They also unveiled the mysterious SOS response in *Escherichia coli* in response to structural DNA damage and published it in a prestigious journal (Dharmalingam and Goldberg, 1980). By a combination of microscopy and Petroff-Hausser cell count method they monitored that exoV degradation of restricted phage DNA leads to SOS response in the host. By restriction mapping technique he could decipher a T4 phage coded anti-restriction endonuclease gene termed as 'arn' (Dharmalingam and Goldberg, 1976b). After striving for seven years to understand the molecular mechanism of T4 phage restriction system he accepted the offer from Government of India and joined the University from where his journey had begun. During his stay at Tufts University, way back in 1976, he performed clean 2D-PAGE experiments, though the separated proteins could not be identified due to unavailability of mass spectrometer (Figure 1). However, the images were stored carefully, are historical documents mark the genesis of his future journey in the area of clinical proteomics (Figure 1).



Figure 1 a: 2D-PAGE autoradiogram of control *E. coli* lysate.

The autoradiogram, which depicts differently expressed proteins upon induction of *E. coli* with unmodified lambda phage, was performed in 1976 at Tufts School of Medicine, Boston (unpublished).

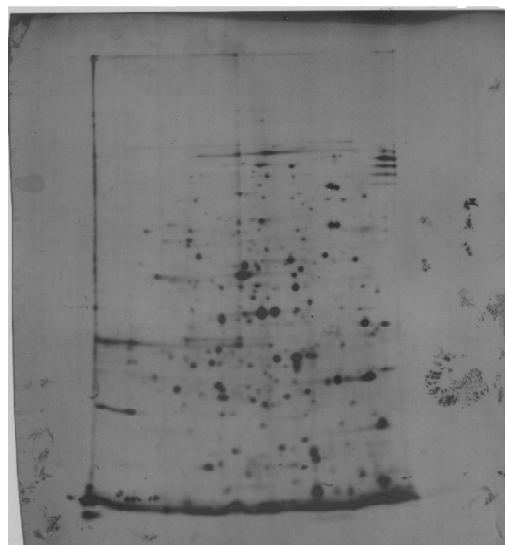


Figure 1 b: 2D-PAGE autoradiogram of unmodified lambda infected *E. coli* cell lysate.

This is one of the oldest gel pictures available from 1976. The proteins could not be identified due to unavailability of mass spectrometer.

An emerging biotechnologist

Continuing with his crave for novelty he again dreamt of 'something new' which ultimately led to the establishment of Biotechnology department

at MKU. His endeavour brought to the world the discovery of unusual DNA amplification in *Streptomyces*. His group reported that a 300 bp segment of *Streptomyces fradiae* genome gets amplified by 30 percent of total genome size (Mathumathi *et al.*, 1990). This DNA amplification also affects protease production and sporulation event in a chloramphenicol resistant mutant. They also recognized a chitinase overproducing mutant of *Streptomyces peucetius* which was defective in daunorubicin biosynthesis (Vetrivel *et al.*, 2000). One of the revolutionary work that he carried out as a collaborative study with University of Geneva, Switzerland was antigen presentation by *Mycobacterial lipoarabinimannans* (LAM). He and his coworkers discovered that these LAMs modulate cytokine signaling in T helper cells by interacting with lipid rafts which causes differentiation of Th0 to Th3 cells (Shabaana *et al.*, 2005). Later, in the subsequent years he started employing "proteomics" techniques which he defines as "a discipline to look at all protein components of a cell in total". He employed MALDI TOF/MS-MS technique to understand the pathogenesis of *Mycobacterium leprae* (Gupta *et al.*, 2007). A single nucleotide polymorphism in the unique small alpha crystalline like heat shock protein of *Mycobacterium leprae* was discovered by his group and they also studied their role in pathogenesis (Rehna *et al.*, 2008).

Contribution to the field of proteomics

Prof. Dharmalingam is one of the pioneer proteomicists in India. One of the hallmarks of his group is clinical proteomics with major focus to identify prognostic biomarkers for eye diseases, diabetic nephropathy, fungal keratitis and glaucoma. He has profiled the proteome of eye samples of Fusarium Keratitis patients (Ananthi *et al.*, 2013). He has used 2D gel electrophoresis as a tool to get a glance at comparative proteome of human male and female tear (Ananthi *et al.*, 2011). In the current years his group has published exoproteome map of *Aspergillus flavus* corneal isolates stating that profusion of multiple proteoforms of alkaline serine protease could be a causative factor for mycotic keratitis (Selvam *et al.*, 2015). Although his current interest is in eye proteomics, he had initially worked to decipher markers for leprosy and had identified alpha-1

glycoprotein as a potential biomarker for monitoring progression of reactive stages of leprosy. Different isoforms of alpha glycoprotein were characterized in this study. He was one of the first to report that proteoforms (protein isoforms) may be important in terms of disease markers by showing significant abundance in one of the isoforms of alpha 2 chain of haptoglobin in erythema nodosum leprosum (Gupta *et al.*, 2010). Thus, he has made immense contribution in augmenting the mass spectrometry facility at MKU. Prof. Dharmalingam has been actively engaged with Proteomics Society, India for a long time and has been a council member of PSI since its inception. He was the convener of a workshop on "Clinical Proteomics: Methods and Applications" held at Aravind Medical Research Foundation, Madurai. He is also the member of the editorial board of PSI newsletter. In 2011, PSI annual meeting and demonstration of proteomics techniques was organized at MKU by Prof. Dharmalingam. To familiarize proteomics he has been keenly working with other PSI members to organize seminar series, workshops, and conferences in different cities in the country.

KD has diversified his scientific voyage as a biochemist, molecular biologist, geneticist and a biotechnologist in an unimpeded manner.

Awards and achievements

Prof. Dharmalingam was awarded the prestigious Shanti Swarup Bhatnagar Prize in 1992 for his pioneering invention of induction of mutagenic DNA repair during restriction of nonglycosylated T4 DNA in *Escherichia coli*. DBT Distinguished Research Professorship was bestowed upon him for decades of prodigious hard work. He joined Aravind Medical Research Foundation as a Director since July 2013. He is a member of the Indian Academy of Sciences and Indian National Academy of Sciences. He is a founder of The Bioinformatics Excellence Centre at MKU. He is actively involved in Biotechnology Research Council and many other committees monitored by DBT. A successful yet humble scientist with more than 200 publications considers himself fortunate enough to have brilliant students throughout his lifetime. He is extremely affectionate towards his students. In spite of

patenting two technologies and giving away five to the industry he always preferred to decline remunerative offers from the industry. He has written many books, 'Concepts in Biotechnology' being one of them that gained quite the success and wide acceptability.

Message to the scientific community

As a responsible scientist he expressed his concern regarding the future of Indian Science quoting that 'Indian scientists should not be followers but leaders.' He also reinforces the idea of 'two way exchange relationship' between a mentor and a PhD student. He believes that 'if you are a good teacher you will be able to learn from a good student'. The adorable man also admits with humility that 'a teacher leaves more impression on a student than a PhD mentor. He believes that students should have conviction to succeed and cultivate the habit of reading irrespective of whichever field they are working in. Being a proteomics researcher he feels it is not just a mere tool rather it is a way of identifying the proteoforms inside a cell and feels that funding agencies should be considerate enough to develop proteomics research in India.

An ardent book lover and perseverant researcher, he is also known for his inexplicable interest in photography and immense love for animals. However, Prof. KD has traversed an arduous journey throughout his scientific career and still is striving to make mass market appeal to 'Proteomics' as a tool. He has taken up large projects from DBT and his team is currently addressing several questions on glaucoma and other eye diseases using quantitative proteomics approach.

Abbreviations

KD: K. Dharmalingam; PhD: doctor of philosophy; MKU: Madurai Kamaraj University; MALDI-TOF/MS: Matrix assisted laser desorption-time of flight/mass spectrometry; PSI: Proteomics Society, India

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